Wernicke's encephalopathy: a more common disease than realised

A neuropathological study of 51 cases

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SUMMARY During a four year period, 51 cases of Wernicke's encephalopathy were diagnosed at necropsy, an incidence of 1.7% of all necropsies performed at the Royal Perth Hospital and by the Perth City coroner. Only seven had been diagnosed during life. Many of the patients died suddenly and unexpectedly, apparently as a result of haemorrhagic brainstem lesions, typical of acute Wernicke's encephalopathy, since no other cause of death was found. There was a high incidence of epilepsy and four patients were hypothermic. The diagnosis of Wernicke's encephalopathy may be missed at necropsy unless the brain is examined histologically. Cerebral atrophy and ventricular dilatation were common findings. This is a more common disease than is generally recognised, one which can be readily treated and, more importantly, prevented by adequate nutrition.

In Australia, a country with a relatively high standard of living, one would expect dietary deficiencies and diseases related to such deficiencies to be uncommon. This does not appear to be the case in regard to vitamin B1 (thiamine) deficiency. One of the common clinicopathological entities associated with thiamine deficiency is Wernicke's encephalopathy or the Wernicke-Korsakoff syndrome. Because of the geographical isolation and relatively small population of Perth (800 000) and because the Neuropathology Department of the Royal Perth Hospital provides a state wide service, we were in the fortunate and perhaps unique situation of being able to examine a relatively high proportion of the brains from those dying in the metropolitan area. Almost 3000 brains were examined in the four year study period. This permitted an accurate assessment of the overall incidence of Wernicke's encephalopathy. There are very few published reports on the incidence of this disease (Cravioto *et al.*, 1961; Victor *et al.*, 1971).

In addition, most of the patients had been seen in one of the major hospitals in the city and their

medical records were available for clinicopathological correlation. It is widely recognised that the nutritional deficiency causing Wernicke's encephalopathy is virtually confined to the alcoholic population.

Materials and methods

Between the years 1973–1976 inclusive, the Department of Neuropathology, Royal Perth Hospital examined 2891 brains postmortem. These brains were derived from two principal sources—from necropsies performed at the Royal Perth Hospital and those performed by the Perth City coroner. All brains were fixed intact for at least two weeks in 10% formol saline. The brains were sectioned coronally in 10 mm slices, the first cut being at the level of the mammillary bodies. In most cases, and in all cases with a history of alcoholism, paraffin sections for histological examination included frontal, temporal, and occipital lobes, the thalami, hypothalamus, and mammillary bodies, basal ganglia, Ammon's horn, cerebellar vermis, and the lateral hemisphere, including the dentate nucleus, the midbrain, pons, and medulla. Several spinal cords were available for examination. Sections were stained using haematoxylin and eosin, Nissl and Weil myelin techniques. Occasional additional techniques such as the Prussian blue

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reaction, Holzer stains, silver impregnations, and oil red O stains were used. The macroscopic and microscopic abnormalities of each brain were tabulated, and estimates of the severity and age of the lesions were made. Hospital records were available for 44 of the 51 cases studied, and an attempt was made to correlate relevant clinical findings with the neuropathology.

Results

Of a total of 2891 brains examined, 51 cases of Wernicke's encephalopathy were diagnosed pathologically, an overall incidence of 1.7%. All but seven of the 51 cases had been seen in one of Perth's major hospitals and Wernicke's encephalopathy had been diagnosed in only seven cases before death. There were 38 men and 13 women and their ages ranged from 30–90 years, the highest incidence being in the fifth decade. Forty-five of the patients were alcoholics. Of the remaining six cases, the clinical histories were inadequate, and the predisposing cause for Wernicke's encephalopathy was not ascertained. One patient was severely malnourished. Undernutrition, defined as at least 15 kg below normal body weight for age, sex, height, and build, was noted in 20 cases. Complete necropsies were performed on all cases. Bronchopneumonia was the most common cause of death (16 cases). In 12 cases the cause of death was undetermined before the neuropathological examination. Ten of these individuals had died suddenly and unexpectedly.

Twenty-seven patients had had liver function tests, and 17 of these were abnormal. The common abnormalities were elevations of serum bilirubin or serum alkaline phosphatase or both and low serum albumin levels. Histologically no abnormality was detected in the liver in 16 of the 51 cases. There were 14 cases with fatty liver, 19 with cirrhosis, and two cases with acute alcoholic hepatitis.

Certain clinical problems may be associated with alcoholism or Wernicke's encephalopathy. Six patients had a peripheral neuropathy. Six patients had had epileptic fits of grand mal type. Four patients died in terminal hypothermia. Central pontine myelinolysis, although not diagnosed clinically, was found in two cases.

NEUROPATHOLOGY

The macroscopic neuropathological findings of the 51 cases are listed in Table 1. The cases were classified as acute, subacute, and chronic, as defined by Victor *et al.* (1971). The mammillary bodies were macroscopically abnormal in 32 cases and histologically in 50 cases. Ten cases showed

Table 1 Macroscopic neuropathological findings

Macroscopic findings	Number of cases
Low brain weight	13*
Cerebral atrophy	11
Ventricular dilatation	12
Mammillary body atrophy	32
Periventricular haemorrhages	5
Cerebellar vermal atrophy	15
Plaques jaunes	8

* Includes two cases of Alzheimer's disease.

acute lesions and 11 showed acute on chronic changes. Macroscopically, five of the 10 acute cases had haemorrhages which involved the walls of the third ventricle, the mammillary bodies, and the floor of the fourth ventricle. The remaining five acute cases had macroscopically normal mammillary bodies. Figure 1 illustrates the severity and extent of the brainstem haemorrhages in one case. Histologically, the acute lesion is characterised by widespread alteration but relatively slight loss of

Fig. 1 Horizontal sections through the midbrain and upper pons show extensive haemorrhage and necrosis centred on the periaqueductal region (A) and extending ventrally into the substantia nigra (SN) on one side.

nerve cells, axis cylinders, and myelin sheaths as well as by proliferation of pleomorphic microglia, prominence of blood vessels, and alteration of astrocytes. Four cases showed subacute lesions and one case subacute on chronic changes. Macroscopically, it is difficult to recognise any abnormality unless haemorrhagic lesions are present. Histologically, the term subacute is applied to a lesion in which a maximum reaction of microglia with macrophage formation has occurred with loss of parenchymal elements. Simultaneously, the vascular changes progress to become the most dramatic feature. The endothelial cell cytoplasm becomes swollen, and the nuclei appear more active. There are increased numbers of endothelial cells and of small capillaries. At this stage it is common to find red blood cells in the Virchow-Robin spaces due either to diapedesis or to rupture of small vessels. There is generally little or no inflammatory reaction. Twenty-five cases were classified as chronic (Table 2). A total of 37 of the

51 cases had chronic lesions either alone or in association with acute or subacute changes. However, in only 32 of these were the mammillary bodies macroscopically abnormal. Typically the mammillary bodies were shrunk, brown, and spongy in appearance (Fig. 2). It should be noted that macroscopically normal mammillary bodies do not exclude the diagnosis of Wernicke's encephalopathy. Histologically, a chronic lesion was taken to be one in which the parenchymal elements had been lost, and in which most of the reactive elements were astrocytic, showing variable degrees of activity. Haemosiderin pigment was recognised around blood vessels—evidence of previous microhaemorrhages. The endstage tissues have a loose vacuolated appearance although there may still be neurones present within these areas. In the quiescent chronic lesions, there is only a slight increase in the normal numbers of blood vessels and the endothelial cells appear normal.

The topographic distribution of the lesions and their incidence of involvement in the 51 cases examined are listed in Table 3. The mammillary bodies were abnormal in 98% of the cases and the periventricular (third ventricular) tissues and periaqueductal structures were abnormal in 60% of the cases. In several cases of acute on chronic Wernicke's encephalopathy, the acute changes were restricted to the hypothalamic structures and the floor of the fourth ventricle while the chronic

Table 2 *Classification of the 51 cases studied*

<i>Age of lesions</i>	<i>Number of cases</i>
Acute	10
Acute on chronic	11
Subacute	4
Subacute on chronic	1
Chronic	25

Fig. 2 The mammillary bodies (arrow) are small, brown, and have a spongy appearance typical of chronic Wernicke's encephalopathy.

Table 3 Topographical distribution of lesions

Site	Incidence %
Mammillary bodies	93
Third ventricular wall	61
Midbrain	61
Pons	50
Thalamus	50
Medulla	33

changes were present in these areas as well as in the medial thalamic nuclei and periaqueductal grey matter.

Decreased brain weight (males less than 1200 grams and females less than 1100 grams) was noted in 13 cases. Two of these cases were found to have Alzheimer's disease. Cerebral atrophy with shrinkage of gyri and widening of sulci was considered significant in 11 cases, and most of these had a slight to moderate symmetrical dilatation of the third and lateral ventricles. Cerebellar vermal atrophy, particularly prominent in the anterior superior cerebellar vermis, was present in 15 cases. However, after histological examination 29 of the 51 cases were found to have significant anterior superior vermal atrophy, with loss of Purkinje cells and proliferation of the Bergmann astrocytes.

Eight of the patients had had previous head injuries with cerebral contusions (plaques jaunes), which were in the classical situations—frontal and temporal poles or on the orbital frontal lobe surfaces or both.

Representative sections from at least three cortical regions were examined in each case and, in addition, silver impregnation techniques were performed in all cases with macroscopic cortical atrophy. There was mild patchy cortical neuronal loss of a nonspecific nature in all cases with macroscopic cortical atrophy but similar changes were seen in many of the other cases.

Discussion

The incidence of Wernicke's encephalopathy in the four year postmortem study from 1973 to 1976 inclusive in Perth, Western Australia, was 1.7% of all brains examined by the neuropathologists of the Royal Perth Hospital. This seems a surprisingly high figure in view of the overall health and nutritional status of Australians. Comparable figures of the postmortem incidence of Wernicke's encephalopathy are scarce in the literature. Victor *et al.* (1971), in their monograph *The Wernicke-Korsakoff Syndrome*, stated that approximately 0.05% of all admissions to the Massachusetts General Hospital were diagnosed as Wernicke's encephalopathy. The incidence at necropsy in Cleveland Metro-

politan General Hospital over the four year period 1963 to 1966 inclusive was 1.9% or 29 cases in 1539 necropsies. Cravioto *et al.* (1961) studied 1600 brains from patients coming to necropsy at the Bellevue Hospital over three years. The incidence of Wernicke's encephalopathy was 1.7%.

It is well recognised that Wernicke's encephalopathy develops as a result of nutritional deficiency of the B group vitamin, thiamine. This presumed aetiological relationship is based on two main observations. Firstly, the chemical analysis of blood from patients with Wernicke's encephalopathy reveals abnormalities consistent with thiamine deficiency (Brin, 1962; Dreyfus, 1962), and secondly, some of the neurological signs respond favourably to the administration of large doses of thiamine, but not the administration of other vitamins (Phillips *et al.*, 1952). Of the 51 patients only one was definitely not an alcoholic. He was an 84 year old man who was severely malnourished because he was physically incapable of looking after himself.

It was surprising how infrequently the diagnosis of Wernicke's encephalopathy had been made clinically before death. Only seven of the 51 cases were diagnosed during life despite the fact that most of the patients had been seen in one of the major teaching hospitals during the last few years of their lives. Why are so few cases of this syndrome diagnosed clinically? Is it possible that the chronic form of the disease can develop after repeated episodes of a subclinical encephalopathy, in which the usual signs of mental confusion, ataxia, ophthalmoplegia, nystagmus, and memory loss might be absent?

The sex incidence (male : female = 3 : 1) is somewhat different to that found by Victor *et al.* (1971), who quoted an incidence of 1.7 to 1. This may reflect a difference in the drinking populations. The age distribution of the two series was similar with a peak incidence in the fifth decade. A disturbing feature is the number of young men and women dying with this disease. There were four cases in their thirties. Three of these patients were aboriginal.

Many alcoholics have additional medical problems both related and unrelated to the alcohol. Approximately 65% of the patients had abnormal liver function studies, and 70% had histological abnormalities of the liver at necropsy which included cirrhosis, fatty liver, and acute alcoholic hepatitis. Wilkinson *et al.* (1971) examined the problem of physical disease in alcoholism in Australia. They studied 1000 patients from an alcoholism clinic, and found that the commonest acute complication was acute alcoholic liver

disease which was present in 25% of all cases, and 9.8% of the cases were cirrhotic.

Bronchopneumonia was the most common cause of death in the 51 cases. Hepatic failure and complications of cirrhosis accounted for another six deaths. In 12 cases the cause of death was said to be undetermined after necropsy. It is of interest to note that 10 of these cases had died suddenly, and unexpectedly. Sudden and unexpected death in alcoholics is a well-known entity, and the various causes include acute toxic effect with respiratory failure (Kaye and Haag, 1957; Derrick, 1967), alcoholic cardiomyopathy with arrhythmias (Laurie, 1971), and the ingestion of alcohol while taking psychotropic drugs causing a severe summation effect (Laurie, 1971). One of the patients in this series died as a result of an alcoholic cardiomyopathy. Tavel *et al.* (1961) in a review of 39 fatalities associated with delirium tremens stated that death occurred suddenly and unexpectedly in four cases, and no cause for death was found in three necropsied cases. Unfortunately, many of the cases in his series had no brain histology performed, and the diagnosis of Wernicke's encephalopathy could well have been missed. Victor *et al.* (1971) also noted the phenomenon of sudden death in patients with delirium tremens. The causative mechanism remains obscure.

Thirty-two of the 51 patients died suddenly but in only 10 instances was the cause of death not evident. Of these, eight had either acute or acute superimposed on chronic Wernicke's encephalopathy. Two of these patients died as a result of their extensive haemorrhagic brainstem lesions which presumably affected the vital medullary centres.

Certain other associated clinical problems seen in alcoholics are worthy of comment. Epilepsy is more common in alcoholics than in the general population. Six of the 51 patients were epileptic. Four of these patients had evidence of previous head injuries (plaques jaunes) which could have been epileptogenic lesions. However, two of these patients also had sclerosis of Ammon's horn. Wilkinson *et al.* (1971) found that the incidence of epilepsy was 7.8% in their study of 1000 alcoholics.

Hypothermia in alcoholics is generally thought to result from exposure, but it may also be a manifestation of acute Wernicke's encephalopathy with damage of the diencephalic thermoregulatory centres. Four patients had significant hypothermia which was not related to exposure. In two instances, the hypothermia was noted after intra-abdominal operations. These two patients remained deeply comatose from immediately after

the operation until death. They had the lesions of acute Wernicke's encephalopathy with extensive haemorrhages in the brainstem and hypothalamic regions. Ackerman (1974), in reviewing the literature from 1945 to 1973, could find only seven cases of Wernicke's encephalopathy with hypothermia. He stressed the importance of recognising this syndrome and treating the patients with parenteral thiamine. This is a medical emergency.

The neuropathology of Wernicke's encephalopathy, has been covered excellently in the monograph of Victor *et al.* (1971). However, it should be emphasised that many cases will be missed at necropsy unless sections are taken for histology from appropriate areas. Only 32 of the 51 cases had macroscopically abnormal mammillary bodies. These are the single most reliable structures to examine histologically to allow a diagnosis to be made. Routine neuropathology is unlikely to answer the main question with regard to this disease—that is, what determines the specific periventricular distribution of the lesions? On the other hand, the macroscopic findings of cerebral atrophy and lateral ventricular dilatation in alcoholics have become major points of interest since computerised tomography was introduced. Fox *et al.* (1976) studied a group of alcoholics using computerised tomography, and showed that one-third had markedly enlarged ventricles as compared to a group of normal control subjects. These findings are comparable with my series in which 24% of the cases had enlarged lateral ventricles. Most of these patients were proven alcoholics. Victor *et al.* (1971) noted enlarged lateral ventricles in 26% of their patients with the Wernicke-Korsakoff syndrome. In a further study in Perth, Western Australia, by Cala *et al.* (1978), the frequency of cerebral and cerebellar atrophy was assessed by computerised tomography in 26 heavy drinkers. Their findings were correlated with clinical deficits, the result of psychometric testing, the alcoholic history, and nutritional status. They found that 73% of the patients had cerebral atrophy and that the degree of cerebral hemisphere atrophy correlated significantly with the impairment of non-dominant hemisphere functions. Similar results were recorded by Brewer and Perrett (1971) who found ventricular enlargement, diagnosed by pneumoencephalography in 73% of a group of 33 alcoholics. The primary cause of this cerebral atrophy with ventricular enlargement has yet to be determined. Fox *et al.* (1976) questioned whether the pathogenesis of the ventricular enlargement could be related to associated liver disease. It is of interest to note that of my 12 patients with enlarged ventricles, seven had nor-

mal liver function studies and normal liver histology at necropsy. It, therefore, seems unlikely that associated liver disease could play a role in the pathogenesis of the cerebral atrophy. Ron (1977) has reviewed the neuropathological, neuroradiological, and psychological findings of brain damage in chronic alcoholism. He concluded that cortical and subcortical atrophy appear to be demonstrable neuroradiologically and at necropsy. A degree of psychometric impairment accompanies these morphological changes, and the presence and severity of the deficit tends to be related to the amount of alcohol consumed and the length of the drinking history.

This disease, Wernicke's encephalopathy, is caused by a nutritional deficiency of vitamin B1 (thiamine) and, in the acute situation, the response to parenteral thiamine is quick and dramatic. More importantly, this disease is potentially preventable, and the group at risk is an obvious one although not readily accessible.

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